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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/462,740 | 04/05/2000 | HIROSHI MURAKAMI | Q57531 | 5460 |

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EXAMINER

PARAS JR, PETER

| ART UNIT | PAPER NUMBER |
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1632

DATE MAILED: 12/27/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/462,740

Applicant(s)

MURAKAMI ET AL.

Examiner

Peter Paras

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 6-8 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 6-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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Applicants' amendment filed on January 22, 2001 has been entered. Claims 1-3 and 6-7 have been amended. Claims 4-5 have been cancelled. New claim 8 has been added. Claims 1-3 and 6-8 are pending and under current examination.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejections of claims 1-3 and 6-7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention have been withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 6-8 as amended or newly added are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The previous

rejection under 112, 1st paragraph is maintained for the reasons of record advanced in the Office action mailed on 7/24/00 on pages 3-8.

Applicant's arguments filed on 1/22/01 have been fully considered but are not found persuasive. Applicants have argued that the Examiner's rejection of record inappropriately requires that the claimed transgenic mammals must be enabled for use in xenotransplantation. Applicants point out that the claims as written do not require that the transgenic mammals be used for xenotransplantation. Applicants assert that any demonstrated utility or any utility accepted by the skilled artisan from understanding the disclosure in view of the prior art is sufficient to fulfill the enablement requirement. Applicants further assert that the instant specification teaches uses other than xenotransplantation for the claimed transgenic mammals. Applicants submit that the results shown in Fig 7 demonstrate that cells from the claimed transgenic mammals may be used in *ex vivo* methods to supplement or substitute for functions of damaged organs or cells of patients. See pages 4-5 of the amendment.

In response, the Examiner maintains that the instant specification has not enabled the claimed transgenic mammals for use in xenotransplantation. Under the enablement requirement the claims must be interpreted in light of the teachings of the specification to determine whether it would require undue experimentation to make and use the invention as claimed. The instant specification is directed to xenotransplantation and use of cells and tissues from the instantly claimed transgenic mammal for xenotransplantation. The industrial uses of the claimed invention outlined on pages 9-11 of the specification relate to xenotransplantation. The instant

specification however has not provided any guidance, teachings, or working examples that demonstrate or otherwise correlate to the use of claimed transgenic mammals in xenotransplantation. See page 5 of the Office action mailed on 7/24/00. Because the instant specification is directed to xenotransplantation of cells or tissues from the claimed transgenic mammals it is not clear how to otherwise use the claimed transgenic mammals. See pages 4-5 of the Office action mailed on 7/24/00. The Examiner maintains that the art of xenotransplantation is unpredictable with respect to suppression of hyperacute rejection in organ transplant recipients. While it is possible to produce transgenic mammals that comprise a transgene of interest, particularly hDAF/CD55, it is not predictable if hDAF/CD55 would be expressed at a level and specificity to allow xenotransplantation of transgenic organs by preventing hyperacute rejection. Furthermore, it is not clear from the teachings of the specification if expression of hDAF/CD55 alone is enough to suppress the complement cascade and prevent hyperacute rejection of a transgenic organ in a recipient. See page 5 and also Kuipers and Artip on page 6 of the Office action mailed on 7/24/00. It is further maintained that the working examples provided by the instant specification are directed only to *in vitro* assays that demonstrate the biological activity of the transgenic hDAF/CD55. The instant specification has not provided any working examples that are directed to xenotransplantation of an organ *in vivo* from the claimed transgenic mammals. In light of such, it is unclear how the *in vitro* experimentation provided by the instant specification correlates to actual transplantation of a transgenic organ from the claimed transgenic mammals. See pages 6-7 of the Office action mailed on 7/24/00.

Accordingly, the previous rejection is maintained for the reasons of record and as discussed in the preceding paragraphs.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The previous rejection of claims 1-3 and 6-7 under 35 U.S.C. 102(b) as being anticipated by Rosengard et al is withdrawn in view of Applicant's amendments to the claims, which now recite the nucleotide sequence set forth in SEQ ID NO: 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The previous rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Rosengard taken with Toyomura is withdrawn.

The following are new grounds of rejection under 35 U.S.C. 103(a):

Claims 1-3 and 6-8 as amended or newly added are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosengard taken with Toyomura (US 6,255,474, July 3, 2001).

The claims are directed to transgenic mammals comprising a transgene encoding human DAF/CD55 operably linked to the porcine complement inhibitor (pMCP) promoter, whose nucleotide sequence is defined in sequence 1, wherein hDAF is expressed in same mammals organs and tissues. For the purposes of prior art rejections the claims are interpreted to being drawn only to the product, transgenic mammals comprising DAF/CD55, and not the intended use of the product.

Rosengard et al teach a transgenic pig which comprises a transgene encoding human DAF/CD55 under the control of its endogenous promoter (page 1325 column 2 paragraph 2, and also Materials and Methods). Patterns of hDAF/CD55 show widespread endothelial cell distribution (page 1326 RESULTS paragraph 2). Expression of hDAF/CD55 was detected in the endothelial cells of the kidney, liver, heart, lung, and aorta (page 1327 paragraph bridging columns 1-2).

Rosengard differs from the claimed invention by not teaching the use of the pMCP promoter to direct expression of the DAF/CD55 transgene.

Toyomura et al teach the cloning and sequencing of a porcine complementary inhibitor cDNA (pMCP) from porcine vascular endothelium. See column 2, and throughout entire document. Toyomura et al expressed human DAF operably linked to the pMCP promoter (as shown in SEQ ID NO: 1) in porcine cells in vitro. See columns 7-8. The promoter of Toyomura is 100% identical to the pMCP promoter sequence,

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particularly bases 4498-5397, recited in the claims. Toyomura et al teach that pMCP is more than 20 times more effective in expressing hDAF than the hDAF promoter. See column 8. Toyomura et al suggest that the pMCP promoter may be useful for the expression of human complement inhibitors in transgenic pigs to reduce rejection observed in the porcine-to-human organ transplantation. See columns 2 and 4.

Accordingly, in view of the teachings of Toyomura et al., it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the transgenic construct of Rosengard by use the pMCP promoter to direct expression of hDAF/CD55 in transgenic mammals with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to achieve high levels of expression of human complement regulatory proteins, including DAF/CD55, in endothelial cells, particularly since Toyomura et al teach that the pCMP promoter more efficiently directs expression of hDAF than the hDAF promoter in porcine cells (see column 8), and more particularly because Toyomura et al has suggested that the pMCP promoter may be used to express human complement inhibitors in transgenic pigs (see columns 2 and 4) .

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

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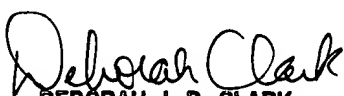
Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

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